LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

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2000-02-03

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852
USA

RE: Comments on Draft Guidance, Pharmacokinetics in patients with impaired hepatic function.

Docket No. 99D-5047

Please find enclosed comments from the Medical Products Agency on the Draft Guidance, Pharmacokinetics in patients with impaired hepatic function: Study design, data analysis, and impact on dosing and labelling.

On behalf of the Medical Products Agency

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Docket No. 99D-5047

Comments on: Draft Guidance for Industry on Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labelling.

General Comments

The Medical Products Agency (MPA) supports the contents of this draft guidance. The MPA also strongly supports the concept referred to in the guidance that the underlying concentration/effect (both desirable and undesirable) relationship needs to be characterised so that rational dosage recommendations can be made in the event of changes in pharmacokinetics in patients with hepatic impairment.

The option of a reduced study design has been proposed. It is our thinking that most Sponsors will opt for this design, accepting the contraindications for severe hepatic impairment that use of such a design entails, since it will be easier and faster to conduct. It is possible that we could end up in the situation where severely hepatically impaired patients have no therapy available, has the FDA considered this implication when proposing the reduced study design?

The MPA feels that different degrees of hepatic impairment should possibly be studied until an effect of the impairment is observed, thus allowing us as regulators to establish a no effect (of hepatic impairment) level. Inspection of our own data base has shown that rarely are severely sick patients studied, even if they are included in studies as Child-Pugh Grade C. A wish to avoid specific dose recommendations or contraindication could tempt the industry to study relatively healthy subjects within the different Child-Pugh groups. The potential problem of extrapolating results from these subjects to the total population is obvious. Furthermore, very few patients, regardless of degree of impairment are studied. We, as regulators, then have to make general recommendations based upon very little and fairly unrepresentative data. The solution to this problem is not immediately obvious, including more patients is one approach but would probably not be easily accepted by Sponsors. In conclusion, if a reduced study design is used to show a lack of a clinically relevant effect in mild to moderately impaired patients, it is important to ensure that the subjects studied represent the entire population, i.e. the majority of the subjects should preferably be on the borderline between moderate and severe.

As is the case with all drugs, in all situations (*e.g.* special populations, drug interactions), what we as regulators can recommend in terms of dosage adjustments is highly dependent upon what dose sizes (and whether they are divisible) the sponsor has developed. Given the increasing marketing pressure for the 'one dose fits all' concept, it may be that our options in terms of dose titration are more limited than we would like them to be. If the Sponsor doesn't have the required dose size needed for dosing in hepatic impairment then should we contraindicate? It is our opinion that those Sponsors without the required dose sizes should be "penalised" in one way or the other.

Specific Comments

Page 3, first paragraph.

The second sentence of this paragraph is interesting for two reasons. First, that the influence of renal failure can be important for drugs that are eliminated hepatically is specifically cited; this appears to be a problem that is not widely recognised by Sponsors and it is good that it has been included here. Second, the interaction between two covariates is specifically stated; as regulators we often have data that address situations where only one covariate in considered (in this case liver impairment), it is important that interactions between covariates are also considered by the Sponsor and which is not something that we often receive information about.

Page 4, second paragraph

We support the use of the Child Pugh category for including patients into the hepatic impairment study. However, we do not feel that the analysis of the results should be restricted to this categorisation. As the FDA discusses at the start of the guidance, this category has it's drawbacks and the results may be more appropriately analysed using one or more different variables (such as S-albumin, bilirubin or prothrombin time).

Page 6, Population PK approach, first bullet point

By preplanned analysis do you mean that the protocol should include a sentence listing liver impairment as one of the covariates to be investigated? Or is something more comprehensive envisaged? The MPA believes that the first option is sufficient and that the latter option is inappropriate.

Page 7, Relationship between measurements of Hepatic Function and PK.

In the second sentence we would suggest replacing the word 'correlations' with 'relationships'. The existence of a correlation does not help regulators decide what to do. Knowledge of the relationship should permit a decision to be made as to what the implications of the effect caused by liver impairment are.

Page 8, first paragraph.

In the past the MPA has also recommended the use of a confidence interval approach in assessing whether a significant change has occurred. Such an approach is adequate if no effect is found, however, we are now starting to question if this approach is adequate if an effect is shown. Our reason for this is that use of confidence intervals does not appropriately address the case where variability in effect (or PK parameter) has increased.

Page 8, second bullet point, point (2).

Whilst it seems reasonable to use the standard 80-125% (70-143%) confidence intervals in the absence of underlying information about the PK/PD relationship, it is difficult to see how such intervals can be used for dosage adjustments if 'bioequivalence' cannot be declared. Often the only dosage adjustment possible is to halve the dose, in which case these intervals are quite narrow. What does the FDA propose to do in such a situation?

Page 11, first paragraph in italics.

The suggested paragraph includes the extent of accumulation on chronic administration; is the FDA suggesting that the Sponsor should predict this if only a singe dose study has been performed?

Page 11, middle paragraph in italics

In the case of severe hepatic impairment there may well be an effect on renal elimination, and the lab values used to categorise renal function may become unreliable in this instance. This paragraph could be modified so that even for renally eliminated drugs, severe hepatic impairment should be contraindicated if it has not been studied.

Page 11, bottom paragraph in italics.

It seems as if this paragraph is not going to suggest the magnitude of dosage reduction that could be required in the event of hepatic impairment with concomitant renal failure. Is this to left up to the prescriber?

Page 12, (c), (i) Wide TI

We believe that the labelling consequences of not having studied the effect of hepatic impairment despite the wide TI should be more severe. This paragraph seems just to result in a 'Precaution' for drugs in this category when the effect of liver impairment hasn't been studied. It could be possible that such generous labelling would encourage Sponsors claim their drug has a wide TI and then not conduct a hepatic impairment study at all, since no contraindication results. The MPA believes that knowledge should be rewarded and lack of knowledge should be penalised and, at the very least, severe hepatic impairment should be contraindicated in this situation.

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